IRF8-dependent DCs play a key role in the regulation of CD8 T cell responses to epithelial-derived antigen in the steady state but not in inflammation

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Along the process of epithelial self-renewal, antigens derived from apoptotic intestinal epithelial cells (IECs) are taken up by antigen presenting cells (APCs), transported to gut-draining lymph nodes and cross-presented to CD8 T cells. In steady state, rapid tolerization of CD8 T cells reactive towards epithelial-derived antigens is crucial to maintain tissue homeostasis. Since IRF8-dependent dendritic dells (IRF8-DCs) have superior cross-presenting capabilities, we aimed to investigate their role in this process. IFABP-tOva mice, expressing the model-antigen Ovalbumin (Ova) in IECs, were used as recipients to set up chimeras using either CD11c-cre.Irf8$^{fl/fl}$ bone marrow, which cannot generate IRF8-DCs, or cre-negative Irf8$^{fl/fl}$ control bone marrow. Whereas transfer of Ova-specific CD8 T cells (OT-I cells) to control chimeras resulted in their rapid tolerization, OT-I cells transferred to CD11c-cre.Irf8$^{fl/fl}$ chimeras spontaneously developed into cytotoxic effector T cells (CTL), causing epithelial destruction and intestinal inflammation. However, when the adjuvant R848 was applied in addition to OT-I transfer, inflammation was triggered in both, CD11c-cre.Irf8$^{fl/fl}$ and control chimeras. This demonstrates that IRF8-DCs are crucial for the rapid tolerization of CD8 T cells reactive towards epithelial-derived antigen in steady state, but are not essential for the induction of CTLs in an inflammatory setting such as found in infection.